1: Cancer Res. 1996 Dec 1;56(23):5319-24. Related Articles, Links

Inhibition of human breast cancer metastasis in nude mice by synthetic glycoamines.

Glinsky GV, Price JE, Glinsky VV, Mossine VV, Kiriakova G, Metcalf JB.

Cancer Research Center, Department of Biochemistry, University of Missouri, Columbia 65201, USA.

We have examined the effect of synthetic low molecular weight glycoamine analogues on the metastasis of MDA-MB-435 human breast carcinoma xenografts growing in the mammary fat pads of nude mice. Initial in vitro screening of a panel of synthetic glycoamines was performed using a clonogenic growth assay in 0.9% agarose. Eight of nine compounds manifested a significant dose-dependent inhibition of colony formation by MDA-MB-435 cells in 0.9% agarose. The relative activity ranks of the compounds, based on ID50S independently determined for each synthetic glycoamine analogue, identified N-(1-deoxy-D-lactulos-1-yl)-L-leucine (Lac-L-Leu), N-(1-deoxy-D-fructos-1-yl)-D-leucine (Fru-D-Leu), N-(1-deoxy-D-fructos-1-yl)-L-phenylalanine, and N-(1-deoxy-D-fructos-1-yl)-L-leucine as the most effective inhibitors of colony formation. Two separate experimental treatment protocols were used to examine the effect of selected synthetic glycoamines on human breast cancer growth and metastasis in athymic nude mice. Group A mice were treated intraperitoneally daily from day 2 after injection of the breast cancer cells until the end of the experiment (17 weeks). In group B, the mice were untreated until the mean tumor diameter was 10 mm, at which time daily i.p. treatment began. After 7 days, the primary tumors were resected, and the mice were treated for an additional 4 weeks (a total of 5 weeks of treatment). The synthetic glycoamines did not have significant antitumor effects, and there was no difference in the tumor incidence or tumor growth rates in mice treated continuously with synthetic glycoamines or PBS. The significant antimetastatic activity of synthetic glycoamines was detected in both experimental treatment protocols. In mice continuously treated with synthetic glycoamines according to protocol A, the incidence of metastasis was decreased 4.6-fold ($P = 0.014$) and 2.7-fold ($P = 0.031$) in mice treated with Fru-D-Leu and Lac-L-Leu, respectively. In mice in protocol B, the incidence of pulmonary metastasis was decreased 1.9-fold ($P = 0.069$) and 2.5-fold ($P = 0.042$) in mice treated with Fru-D-Leu and Lac-L-Leu, respectively. Correspondingly, the average number of spontaneous pulmonary metastases was reduced from 37 in control mice to 0.2 ($P = 0.005$) and 0.9 ($P < 0.02$) in mice treated according to the protocol A with Fru-D-Leu and Lac-L-Leu, respectively. Treatment of mice with N-(1-deoxy-D-fructos-1-yl)-L-leucine did not have significant antimetastatic effects, and no reduction in metastasis incidence or number was noted in mice treated with this synthetic glycoamine analogue. The treated animals had no apparent toxicity from chronic

daily injection (up to 17 weeks of treatment) of synthetic glycoamines, and no obvious pathology was noted in the histological slides of the livers, kidneys, or spleens of the treated mice. Therefore, we have identified two synthetic glycoamines (Fru-D-Leu and Lac-L-Leu) that were the effective inhibitors of spontaneous human breast cancer metastasis in nude mice. Potential mechanisms for antimetastatic activity of synthetic glycoamines may include the inhibition of beta-galectin-mediated homotypic cancer cell aggregation and induction of apoptosis in target cells.

PMID: 8968076 [PubMed - indexed for MEDLINE]
